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EXAMINER
WHITEMAN, BRIAN A

ART UNIT	PAPER NUMBER
1635	12

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Please find below and/or attached an Office communication concerning this application or proceeding.

SM

Office Action Summary	Application No.	Applicant(s)	
	09/606,804	LEE, AMY S.	
	Examiner	Art Unit	
	Brian Whiteman	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 November 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-62* is/are pending in the application.

4a) Of the above claim(s) *10-14,17-21,25,44,47-62* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9,15,16,22-24,26-43,45 and 46* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *28 June 2000* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Non-Final Rejection

The Non-Final Rejection in paper no. 11 mailed on 1/15/03 has been vacated. The only difference between the office action in paper no. 11 and the instant action is the addition of an analysis of priority for claims 1-9, 15-16, 22-24, 26-43, and 45-46. A PTO-892 is not enclosed with the instant action because a PTO-892 listing the publications cited herein was submitted in paper no. 11, mailed on 1/15/03.

Claims 1-62 are pending examination.

Applicant's election without traverse of Group I and species systemic (claim 43) and lung cancer (claim 46) in Paper No. 10 is acknowledged.

Applicants in an apparent oversight forgot to elect an additional species as set forth on page 8 of paper no. 9. Examiner contacted applicant's representative, Dr. Reed about the oversight on 12/30/02 and applicant's representative elected biologically active protein (claim 6) without traverse.

After further consideration, the restriction was improperly made because claims 18-21 should not have been in Group I because of the reasons set forth in paper no. 9. The claims should have been with Group II. Examiner contacted applicant's representative, Dr. Reed about

removing claims 18-21 from the elected group and placing them in Group II. Dr. Reed agreed with the new grouping of the claims.

In addition, in view of MPEP 803.02, claims 26-35 are placed in both group I and group II. Group I would encompass claims 26-35 being directed to claim 1 and claim 22. Group II would encompass claims 26-35 depending on claim 17.

Claims 17-21, 44, and 47-62 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a non-elected invention and claims 10-14 and 25 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a non-elected species there being no allowable generic or linking claim. Election was made **without** traverse in Paper No. 10.

Priority

Applicant's claim for domestic priority under 35 U.S.C. 119(e) is acknowledged. However, the provisional application upon which priority is claimed fails to provide adequate support under 35 U.S.C. 112 for claims of this application.

The reasons for why claims 1-9, 15-16, 22-24, 26-43 and 45-46 are not supported by the provisional 60/141,505 as discussed herein:

The provisional is a journal article (Cancer Research 59:3100-3106, 1999) directed to using a tumor cell line comprising a retroviral vector comprising a rat grp78 promoter operatively linked to a thymidine kinase gene for suicide gene therapy of murine Fibrosarcoma.

Claims 1, 15-16, 22, 23, and 24: The provisional provides support under 112 first paragraph written description and enablement, for the rat grp78 promoter operatively linked to a

thymidine kinase gene. However, the provisional does not provide sufficient written description for a representative number of stress-responsive non-coding regulatory sequence comprising at least two ERSE as set forth in SEQ ID NO: 1. In addition, the provisional and the art of record do not disclose how to make and/or use a genus of the claimed nucleic acid construct because only the rat grp 78 promoter is taught and the rat promoter alone is not a representative of the claimed genus. The provisional does not provide adequate description for correlating the structure and function of the rat grp78 promoter to the claimed genus of stress-responsive non-coding regulatory sequences. In addition, the claims encompass full-length genes and cDNAs that are not described by the provisional.

Claim 2: The provisional provides support for how to make and/or use the rat grp78 promoter. The provisional does not provide written description for a genus of regulatory sequence comprising at least two ERSE derived from any grp78 promoter sequence. The provisional and the art of record do not disclose how to make or obtain a representative number of species of grp78 promoter sequences because the rat grp78 promoter was the only grp78 promoter known at the time the provisional was filed.

Claim 3: The provisional does not provide support for a grp78 promoter sequence comprising a sequence from about 3000 base pairs 5' of the site of initiation of transcription of the grp78 coding sequence to 200 base pairs 3' of the site of initiation of the grp78 coding sequence. The provisional only describes using a 695-bp rat grp78 promoter (see page 3101).

Claim 4: The provisional does not provide support for using any transcriptional and translational initiation region other than the regions encoded in the rat grp78 promoter sequence. The claimed invention embraces making and using the promoter in a heterologous construct and

the provisional does not provide written support nor enablement for the full breadth of the claimed embodiment.

Claims 6-9: The provisional provides support for operatively linking a suicide gene (HSV thymidine kinase) to the rat grp78 promoter.

Claims 26-30: The provisional does not provide written support for making any type of recombinant vector other than a retroviral vector. The provisional only teaches how to make and use a retroviral vector.

Claims 31-35: The provisional does not provides written support nor enablement for making any type of pharmaceutical composition set forth in claims 31-35. The provisional teaches ex vivo administration of a tumor cell line comprising a retrovirus vector comprising HSV-tk operatively linked to the rat grp78 promoter to a mouse. The provisional does not disclose how to make the composition selected from controlled release formulation, liposomal formulation, or a lyophilized form and such that the composition would function *in vivo*. In view of the art of record, it is not apparent how a tumor cell line can be reasonably correlated to any claimed pharmaceutically acceptable carrier.

Claims 36-43: The provisional teaches *ex vivo* administration of a tumor cell line comprising a retrovirus vector comprising HSV-tk operatively linked to the rat grp78 promoter to a mouse. However, the provisional does not provide sufficient guidance or factual evidence for systemically, locally, or topically administering a pharmaceutical composition comprising the DNA construct of claim 1 for treating any type of neoplastic disorder. In addition, the provisional does not provide support for treating any type of neoplastic disorder in any mammal other than a glucose-deprived tumor in a mouse.

Claims 45-46: The provisional provides support for using a tumor cell line comprising a retroviral vector comprising the rat grp78 promoter operatively linked to a thymidine kinase gene for suicide gene therapy of murine Fibrosarcoma. The provisional does not provide sufficient guidance and/or factual evidence for one skilled in the art to reasonably correlate using a tumor cell comprising a retroviral vector comprising a nucleic acid construct comprising the rat grp78 promoter operatively linked to a thymidine kinase gene to using a recombinant vector comprising the claimed nucleic acid construct as set forth in claim 1 for *in vivo* gene therapy of a neoplastic disorder. In addition, the provisional does not provide support for treating any type of neoplastic disorder in any mammal other than a glucose-deprived tumor in a mouse.

The international search report and international examination report have been considered.

Drawings

New corrected drawings are required in this application because of the objection by the draftsperson. Applicant is advised to employ the services of a competent patent draftsperson outside the Office, as the U.S. Patent and Trademark Office no longer prepares new drawings. The corrected drawings are required in reply to the Office action to avoid abandonment of the application. The requirement for corrected drawings will not be held in abeyance.

Color photographs and color drawings are acceptable only for examination purposes unless a petition filed under 37 CFR 1.84(a)(2) is granted permitting their use as acceptable

drawings. In the event that applicant wishes to use the drawings currently on file as acceptable drawings, a petition must be filed for acceptance of the color photographs or color drawings as acceptable drawings. Any such petition must be accompanied by the appropriate fee set forth in 37 CFR 1.17(h), three sets of color drawings or color photographs, as appropriate, and an amendment to the first paragraph of the brief description of the drawings section of the specification which states:

The patent or application file contains at least one drawing executed in color. Copies of this patent or patent application publication with color drawing(s) will be provided by the U.S. Patent and Trademark Office upon request and payment of the necessary fee.

Color photographs will be accepted if the conditions for accepting color drawings have been satisfied.

Claim Objections

Claims 26-37 are objected to because of the following informalities: depend on a non-elected claim (claim 17). Suggest removing claim 17 from the pending claims.

Claim 8 is objected to because of the following informalities: using "or" after the phrase "a group consisting of" (See MPEP 2173.05(h)). Suggest replacing "or" with -- and --.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-9, 15, 16, 22-24, 26-43, and 45-46 rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1, 4-9, 15, 16, 22-24, 26-43, and 45-46 as best understood, are readable on a genus of a nucleic acid construct comprising: at least one stress-responsive non-coding regulatory sequence comprising at least two endoplasmic reticulum stress elements (ERSE) as set forth in SEQ ID NO: 1, wherein the genus of one stress-responsive non-coding regulatory sequence comprising at least two endoplasmic reticulum stress elements (ERSE) as set forth in SEQ ID NO: 1 is not claimed in a specific biochemical or molecular structure that could be envisioned by one skilled in the art at the time the invention was made are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 2, 3, 22-24, 26-43, 45-46 as best understood, are readable on a genus of a grp78 promoter, wherein the genus of grp78 promoter is not claimed in a specific biochemical or molecular structure that could be envisioned by one skilled in the art at the time the invention was made are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The specification contemplates using a genus of stress-responsive non-coding regulatory sequence comprising at least two endoplasmic reticulum stress elements (ERSE) as set forth in SEQ ID NO: 1 and/or a genus of a grp78 promoter. The as-filed specification provides sufficient description of a species of a glucose responsive protein 78 (grp) promoter sequence from a rat that has two ERSE as set forth in SEQ ID NO: 1. However, the specification does not provide sufficient description of a representative number of nucleotide sequences comprising a stress-responsive non-coding regulatory sequence comprising at least two endoplasmic reticulum stress elements (ERSE) as set forth in SEQ ID NO: and/or sufficient description of a representative number of grp78 promoters to sufficiently describe the genus of grp78 promoters. It is apparent that on the basis of applicant's disclosure, an adequate written description of the invention defined by the claims requires more than a mere statement that it is part of the invention and reference to potential methods and/or molecular structures of molecules that are essential for the genus of grp78 promoters and/or the genus of stress-responsive non-coding regulatory sequences comprising at least two endoplasmic reticulum stress elements (ERSE) as set forth in SEQ ID NO: 1 as claimed; what is required is the knowledge in the prior art and/or a description as to the availability of a representative number of species of biochemical or molecular structures of non-regulatory sequences and/or grp78 promoters that must exhibit the disclosed biological functions as contemplated by the claims.

It is not sufficient to support the present claimed invention directed to a genus of grp78 promoters and/or a genus of stress-responsive non-coding regulatory sequence comprising at least two endoplasmic reticulum stress elements (ERSE) as set forth in SEQ ID NO: 1. The claimed invention as a whole is not adequately described if the claims require essential or critical

elements, which are not adequately described in the specification and which is not conventional in the art as of applicant's effective filing date. Claiming a genus of grp78 promoters and/or a genus of a stress-responsive non-coding regulatory sequence that must possess the biological properties as contemplated by applicant's disclosure without defining what means will do so is not in compliance with the written description requirement. Rather, it is an attempt to preempt the future before it has arrived. (See *Fiers v. Revel*, 25 USPQ2d 1601 (CA FC 1993) and *Regents of the Univ. Calif. v. Eli Lilly & Co.*, 43 USPQ2d 1398 (CA FC, 1997)). Possession may be shown by actual reduction to practice, clear depiction of the invention in a detailed drawing, or by describing the invention with sufficient relevant identifying characteristics such that a person skilled in the art would recognize that the inventor had possession of the claimed invention. Pfaff v. Wells Electronics, Inc., 48 USPQ2d 1641, 1646 (1998). The skilled artisan cannot envision the detailed structure of a genus of grp78 promoters and/or a genus of a stress-responsive non-coding regulatory sequence that must exhibit the contemplated biological functions, and therefore, conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the structures and/or methods disclosed in the as-filed specification. Thus, in view of the reasons set forth above, one skilled in the art at the time the invention was made would not have recognized that applicant was in possession of the claimed invention as presently claimed.

Claims 1-9, 15-16, 22-24, 26-43, and 45-46 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for making a nucleic acid construct comprising a functional promoter comprising at least one stress-responsive non-coding

regulatory sequence comprising at least two endoplasmic reticulum stress elements (ERSE) as set forth in SEQ ID NO: 1 from a rat grp78 coding sequence and using a vector comprising the construct for reducing a cell proliferative disorder associated with glucose starvation in a subject, does not reasonably provide enablement making and using a genus of a nucleic acid construct comprising at least one stress responsive non-coding regulatory sequence and treating any cell proliferative disorder in a subject. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Specifically, since the claimed invention is not supported by a sufficient written description (for possession of a genus of a stress-responsive non-coding regulatory sequence and/or a genus of grp78 promoters), particularly in view of the reasons set forth above, one skilled in the art would not have known how to use and make the claimed invention so that it would operate as intended, e.g. making a nucleic acid construct for use in treating a cell proliferative disorder in a subject.

> Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized in In re Wands, 858 F.2d 731, 8USPQ2d 1400 (Fed. Cir. 1988). They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The invention is directed to producing a nucleic acid construct comprising at least one stress-responsive non-coding regulatory sequence comprising at least two ERSE as set forth in SEQ ID NO: 1 and a heterologous nucleic acid sequence operatively linked to the regulatory sequence and using the construct in a method of treating a cell proliferative disorder in a subject.

In addition, with respect to claim 3, the specification does not disclose a nucleotide sequence or SEQ ID NO: for one skilled in the art to make and use the claimed embodiment.

The specification does not provide sufficient guidance for one skilled in the art to reasonably determine which grp78 coding sequence is being defined by the claim. The art of record displays that here are several sequences that contain a grp78 coding sequence (rat, mouse, human, C.elegan, etc.) and each sequence is not the same length in base pairs. Thus, in view of the lack of guidance provided by the specification and the numerous nucleotide sequences containing a grp78 coding sequence, it would take one skilled in the art an undue amount of experimentation to practice the claimed embodiment.

Furthermore, and with respect to claim 36-43 and 45-46 directed to any vector useful for gene therapy and directed to treating a cell proliferative disorder in a subject; the state of the art in 1998, exemplified Anderson et al., *Nature*, Vol. 392, pp. 25-30, April 1998, displays major consideration for any gene transfer or any DNA therapy protocol involve issues that include:

1) The type of vector and amount of DNA constructs to be administered,

2) The route and time course of administration, the sites of administration, and successful uptake of the claimed DNA at the target site;

3) The trafficking of the genetic material within cellular organelles, the rate of degradation of the DNA, the level of mRNA produced, the stability of the mRNA product, the amount and stability of the protein produced, and

4) What amount of the expressed proteins considered to be therapeutically effective for a DNA therapy method.

In addition, all of these issues differ dramatically based on the specific vector used, the route of administration, the animal being treated, therapeutically effective amount of the DNA, and the disease being treated.

Anderson teaches that gene therapy is a powerful new technology that still requires several years before it will make a noticeable impact on the treatment of disease, and that several major deficiencies still exist including poor delivery systems, both viral and non-viral, and poor gene expression after genes are delivered (pp. 25-30).

Anderson further teaches that the reason for the low efficiency of gene transfer and expression in human patients is that we still lack the basis understanding of how vectors should be constructed what regulatory sequences are appropriated for which cell types (page 30, column 1, last paragraph). Furthermore, Verma, *Nature*, Vol. 389, pages 239-242, 1997, indicates that factors including the nature of the diseases and/or disorders, the nature of a DNA and/or target tissue, and a delivery system and/or amounts of the DNA complexes employed in the delivery system that would generate a therapeutic effect *in vivo* must be considered for any gene therapy method to be successful (page 238, columns 1 and 2).

In further view of the doubts expressed above by Anderson and Verma, the state of the art at the time the application was filed and currently for cancer gene therapy as discussed by Vile et al., (*Gene Therapy*, Vol. 7, pp. 2-8, 2000). Vile teaches:

> The problems which gene therapy for cancer will take into the next millennium focus far less on the choice of therapeutic gene(s) to be used than on the means of delivering them. There is already a battery of genes that we know are very effective in killing cells, if they can be expressed at the right site and at appropriate levels. Nonetheless, until the perfect vector is developed, the choice of gene will remain crucially important in order to compensate for the deficiencies of the vectors we currently have available (page 2, 1st paragraph, left column). Whatever its mechanism, no single genes can be a serious contender unless it has a demonstrable bystander effect (page 2, right column). The requirement for such a bystander effect stems directly from the poor delivery efficiency provided by current vectors (page 2, right column).
>
> A genuine ability to target delivery systems to tumor cells distributed widely throughout the body of a patient would simultaneously increase real titers and efficacy. In truth, no such systemically targeted vectors exist yet. Injection of vectors into the bloodstream for

> the treatment of cancer requires not only that the vectors be targeted (to infect only tumor cells) but also that they by protected (from degradation, sequestration or immune attack) for long periods of time so that they can reach the appropriate sites for infection. Moreover, having reached such sites, the vectors must be able to penetrate into the tumor from the bloodstream before carrying out their targeted infection (page 4, bottom left column and top right column).
>
> Even the highest titer system is clearly not high enough yet to cure even local tumors. Therefore, there is a clear need to explore and exploit, a range of alternative options. The development of replication vectors for cancer gene therapy is the inevitable consequence of data from the early clinical trials. So far, a substantial therapeutic gap still exists between the overlap of the efficacy provided by, on the other hand, the potency of the therapeutic gene(s) and on the other, the efficiency of gene delivery provided by the vector. Only when these two 'therapeutic domains' approach each other will clinical efficacy result.

The specification provides sufficient guidance for making a vector comprising a nucleic acid construct comprising a grp78 promoter sequence or a truncated rat grp78 promoter sequence and using the vector in a method of reducing a cell proliferative disorder associated with glucose starvation in a subject comprising directly administering the vector to cells involved in the proliferative disorder. However, the breadth of term "treating" encompasses curing and preventing (see page 46) and in view of the In Re Wands Factors the full breadth of the term is not considered enabled. There are several problems with gene therapy and the specification does not provide sufficient guidance for how to overcome these problems, including the transient nature of gene therapy or what cells need to be targeted in order to prevent a cell proliferative disorder in a subject. In addition, the specification and art of record teach that the grp78 promoter is the major stress-inducible protein in cells having glucose starvation (IDS, Gazit et al. Cancer Research, Vol. 59:3100-3106, 1999). The disclosure does not provide sufficient guidance for how to use the claimed vector to treat cells that are not undergoing glucose starvation (e.g. slow growing tumors have a sufficient blood supply and do not experience

glucose starvation). The state of the art cites that, "the spontaneous behavior of human tumors is somewhat different for that of malignant cells *in vitro*, and from that of experimental tumors in animal models" (Gomez-Navarro et al., *European Journal of Cancer*, Vol. 35, pp. 868, Table 1, 1999). Even if a therapeutic response using an *ex vivo* method of gene therapy for cancer in an experimental murine model using transfected cancer cells has been shown in the as-filed specification, it is not apparent as to how it is reasonably extrapolated to the full scope of the claimed invention, encompassing treating any cell proliferative disorder in a subject. Thus, the full scope of the claimed methods is not considered enabled.

Furthermore, claims 36-42 and 45-46 read on using any route of administration and claim 43 is directed to systemic administration to target cells involved in a proliferative disorder in a subject. It would take one skilled in the art an undue amount of experimentation to determine what route of administration (*e.g.* intravenous, dermal, nasal, rectal, vaginal, inhalation, or topical administration) other than direct administration would result in a therapeutic response using the claimed vectors. The specification administers cancer cells transfected with retroviral vectors comprising a truncated grp 78 promoter operatively linked to a heterologous nucleic acid sequence to the shoulder of mice (page 72). The state of the art for the route of administration for gene therapy as exemplified by Verma, *Nature*, Vol. 389, pages 239-242, 1997, indicates that factors including the nature of the diseases and/or disorders, the nature of a DNA and/or target tissue, and a delivery system and/or amounts of the DNA complexes employed in the delivery system that would generate a therapeutic effect *in vivo* must be considered for any gene therapy method to be successful (page 238, columns 1 and 2). In addition, Vile teaches that there are no known vectors that can be used for systemically treating cancer in a subject (page 4). In view of

the state of the art and the lack of guidance provided by the specification for using any route of delivery other than direct administration, it is not apparent to one skilled in the art how to reasonably extrapolate from direct administration to any other route of administration to generate a therapeutic response in reducing a proliferative disorder in a subject.

As a result, it is not apparent how one skilled in the art determines, without undue experimentation, which of the claimed nucleic acid constructs generate a therapeutic effect (treating or preventing), how is it apparent as to how one skilled in the art, without any undue experimentation, practices any nucleic acid therapy method as contemplated by the claims, particularly given the unpredictability of nucleic acid therapy as a whole and/or the doubts expressed in the art of record.

In conclusion, the as-filed specification and claims coupled with the state of the art at the time the invention was made only provide sufficient guidance and/or evidence to reasonably enabled for making a vector comprising a nucleic acid construct comprising a grp78 promoter sequence from a rat grp78 and using the vector in a method of reducing a cell proliferative disorder associated with glucose starvation in a subject comprising directly administering the vector to cells involved in the proliferative disorder. Given that gene therapy wherein any carrier is employed to correct a disease or a medical condition in any mammal was unpredictable at the time the invention was made, and given the lack of sufficient guidance as to a gene therapy effect produced by any gene delivery vector cited in the claims, one skilled in the art would have to engage in a large quantity of experimentation in order to practice the claimed invention based on the applicant's disclosure and the unpredictability of gene therapy.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claims 2, 3, 23, 36-43 and 45-46 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 2 recites the limitation "the glucose responsive protein 78 promoter" in line 14, page 85. There is insufficient antecedent basis for this limitation in the claim.

Claim 3 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential structural cooperative relationships of elements, such omission amounting to a gap between the necessary structural connections. See MPEP § 2172.01. The omitted structural cooperative relationship is: the metes and bounds of what constitutes a sequence from about 3,000 base pairs 5' of the site of initiation of transcription of the grp78 coding sequence to 200 base pairs 3' of the site of initiation of the grp78 coding sequence. The disclosure does not define the metes and bounds for what grp78 sequence is being claimed and what base pairs are being claimed. The specification cites a rat grp78 promoter sequence and uses a truncated rat grp78 promote sequence, but the art of record teaches that there are several other grp78 sequences (human, C.elegan, mouse) with different base pair length. Thus, it is not apparent what base pairs of the grp78 coding sequence are being defined.

Claim 23 recites the limitation "the detectable marker" in line 17, page 89. There is insufficient antecedent basis for this limitation in the claim.

Claims 36-43 and 45-46 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. Claims 36-43 and 45-46 are indefinite in their incomplete recitation of

method steps that do not clearly relate back to their respective preambles, reciting e.g. a method of providing increased transcription (claim 36); a method for inhibiting proliferation (claim 37); or methods for treating cell proliferation disorder (claims 38-43 and 45-46). Specifically, the claims are essentially limited to the step of introducing a nucleic acid without any further reference to the claimed objective(s) or methods in the recited preamble.

Claim Rejections - 35 USC § 102

As stated above the provisional application fails to provide support for the generic embodiments of the claimed invention. Gazit anticipates the broader scope of the claimed invention, which is not disclosed in the Gazit publication.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 1, 2, 4-9, 15-16, 22-24, 26-29, 31, 35-40, 42-43, and 45 are rejected under 35 U.S.C. 102(a) as being anticipated by Gazit et al. (IDS, Cancer Research 59:3100-3106, July 1, 1999). Gazit teaches *ex vivo* administration of a tumor cell line transduced with a retroviral vector comprising a grp78 promoter comprising grp78 regulatory sequence modified to contain 3 ERSE operably linked to HSV tk effective for reducing a cell proliferative disorder in a mouse (pages 3103-3105).

MPEP 2132.01 regarding 35 U.S.C. 102(a) states: "Where the applicants is one of the co-authors of a publication cited against his or her application, the publication may be removed

as a reference by the filing of affidavits made out by the other authors establishing that the relevant portions of the publication originated from, applicant." "The rejection can also be overcome by submission of a specific declaration by the applicant establishing that the article is describing applicant's own work." "However, if there is evidence that the co-author has refused to disclaim inventorship and believes himself or herself to be an inventor, applicant's affidavit will not be enough to establish that applicant is the sole inventor and the rejection will stand." "It is possible to overcome the rejection by adding the co-authors as inventors to the application if the requirements of 35 U.S.C. 116, third paragraph are met."

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or non-obviousness.

Claims 1-2, 4-10, 15, 16, 22-24, 26-29, 31-42, and 45-46 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gazit et al. (IDS, Cancer Research, 55:1660-1663, 1995) taken with Walther et al. (IDS, Molecular Biotechnology, 6:267-286, 1996) in further view of Mullen (IDS, Pharmac. Ther. 63:199-207, 1994). Gazit teaches that a 600-base pair subfragment of grp78 promoter used as an internal promoter within a retroviral vector is able to confer high level of expression of a reporter gene in a murine fibrosarcoma *in vivo* (page 1663). Gazit teaches that since most anticancer agents are extremely toxic when expressed at high levels in normal cells, the discovery of grp78 with stringently enhanced expression in a tumor environment could be useful in cancer gene therapy. However, Gazit does not specifically teach a vector comprising a grp promoter operatively linked to a heterologous sequence encoding an enzyme and using the vector in a method of pro-drug cancer gene therapy in an animal.

However, at the time the invention was made, cancer pro-drug gene therapy was well known to one ordinary skill in the art. Walther et al. reviews methodologies for targeted vectors used in cancer gene therapy and teaches the advantaged of vectors comprising a therapeutic gene operably linked to the grp78 promoter (page 280-281). In addition, Mullen teaches delivery of suicide genes *in vivo* using a viral vector (page 202-203).

At the time the invention was made it would have been *prima facie* obvious for a person of ordinary skill to make a vector comprising a nucleic acid encoding an enzyme that converts a non-therapeutically effective compound to a therapeutically effective compound operatively linked to the grp78 promoter. One of ordinary skill in the art would have been motivated to make the vector because Gazit and Walther teach the advantages of using the grp78 promoter in a vector for cancer gene therapy.

In addition, at the time the invention was made it would have been *prima facie* obvious for a person of ordinary skill to use the claimed vector in a method of prodrug cancer gene therapy. One of ordinary skill in the art would have been motivated to use the vector because the grp78 promoter confers high level of expression of a gene in a murine fibrosarcoma *in vivo*.

Therefore the invention as a whole would have been *prima facie* obvious to one ordinary skill in the art at the time the invention was made.

NOTE: Lee (US Patent No: 5,196,523) is cited on the 892 because she teaches a regulatory sequence for a glucose regulated protein can be used to produce a vector comprising the sequence and a desired DNA sequence and the resulting vector can be induced by high levels of glucose starvation. The patent can be used in the 103(a) rejection set forth above.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brian Whiteman whose telephone number is (703) 305-0775. The examiner can normally be reached on Monday through Friday from 7:00 to 4:00 (Eastern Standard Time), with alternating Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader, SPE - Art Unit 1635, can be reached at (703) 308-0447.

Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (703) 308-4556.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

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